# INTERNATIONAL SEARCH REPORT

International application No
PCT/US04/35929

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/68
US CL : 435/6, 91.2
According to International Patent Classification (IPC or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6, 91.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | BIANCHI et al. Large Amounts of Cell-free Fetal DNA are present in Amniotic Fluid Clinical Chemistry, 2QQI, Vol. 47, No. 10, pages 1867-1869. | 1-3, 5-6, 12-15, 19, 22, 25-30, 34, 38<br>---<br>4, 16-18, 55-59, 97-102, 115-125 |
| X<br>---<br>Y | LAPIERRE et al. Analysis of uncultured amniocytes by comparative genomic hybridization: a prospective prenatal study. Prenatal Diagnosis, 2000, Vol. 20, pages 123-131. | 1,2, 4, 14-16, 19, 21-32, 34, 38<br>---<br>7-11, 21, 43-58, 60-73, 75, 79, 84-88, 90-127 |
| Y | VELTMAN et al. High-Throughput Analysis of Subtelomeric Chromosome Rearrangements by Use of Array-Based Comparative Genomic Hybridization. American Journal of Human Genetics, 09 April 2002, Vol. 70, pages 1269-1276. | 7-11, 21, 43-58, 60-73, 75, 79, 84-88, 90-127 |

☒ Further documents are listed in the continuation of Box C. D See patent family annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
15 November 2005 (15.11.2005)

Date of mailing of the international search report
1a DEC 2005

Name and mailing address of the ISA/US
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FormPCT/ISA/210 (second sheet) (April 2005)

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | PINKEL et al. High resolution analysis of DNA copy number variation using comparative genomic hybridization to microarrays. Nature Genetics, 20 October 1998, Vol. 20, pages 207-211. | 7-11, 21, 43-58, 60-73, 75, 79, 84-88, 90--127 |

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**Box No. π Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. in Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. **D** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: all: 1-29, 31, 32, 34, 38, 43-70, 72, 73, 75, 84-88, 90-127; part: 30 and 71

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐

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## BOX III OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claims 1-127, drawn to methods for prenatal diagnosis

Group 2, claims 128-137, drawn to kits comprising materials and an array

Further lack of unity regarding species applied to each group

species regarding chromosomal abnormalities

i extra chromosome 21
ii missing chromosome 21
m extra portion of chromosome 21
IV missing portion of chromosome 21
v missing portion of chromosome 31
vi rearrangement of chromosome 21
vii extra chromosome 13
viii extra chromosome 18
Ix extra chromosome X
x extra chromosome Y
xi a chromosomal aberration involving chromosome 1
xii a deletion of chromosomal portion 1q21
\ui a deletion of chromosome portion 4p16
xiv an aberration involving chromosome 5
xv a deletion on chromosome 5
xvi an aberration involving chromosome 7
xvii a deletion of 7q11 23
xviii an aberration involving chromosome 8
xix a translocation involving chromosome 9 and chromosome 22
xx an aberration involving chromosome 11
xxi a deletion of chromosome portion 13q15
xxii a deletion of chromosome portion 15q11-q13
xxiii deletion of chromosome 15q21 1
xxiv deletion of chromosome portion 16p13 3
xxv deletion of portion 17p11 2
xxvi deletion of portion 17p13 3
xx\ii aberration involving chromosome 19
xx\iin deletion of chromosome portion 22q11
xxix aberration involving chromosome X

species regarding disease or condition
xxx disease associated with aneuploidy
xxxi Down syndrome
xxxii Patau syndrome
xxxiii Edward syndrome
xxxiv Turner syndrome
xxxv Klinefelter syndrome
xxxvi XYY disease
xxxvii X-linked disorder
xxxviii Hemophilia A
xxxix Duchenne muscular dystrophy
xl Lesch-Nyhan syndrome
xli severe combined immunodeficiency
xlii Fragile X-syndrome
xliii disease associated with microdeletion/microduplication syndrome
xliv Prader-Willi syndrome
xlv Angelman syndrome
xlvi DiGeorge syndrome
xlvii Smith-Magems syndrome
xlviii Rubmstem-Taybi syndrome
xlix Miller-Dieker syndrome
l Williams syndrome
li Charcot-Ma π e-Tooth syndrome
lii disease associated with subtelome π c rearrangement
liii Cn du Chat syndrome
liv Retinoblastoma
lv Wolf-Hirschhorn syndrome
lvi Wilms tumor
lvii spinobulbar muscular atrophy
lviii cystic fibrosis
lix Gaucher disease
lx Marfan syndrome
lxi sickle cell anemia

The first named which will be searched in accordance with the PCT rules is group 1, species group 1, regarding species (i) for the chromosomal aberration and species (xxx) for the disease or condition Thus, the claims searched with the mam invention will be claims 1-29, 31, 32, 34, 38, 43-70, 72, 73, 75, 79, 84-88, 90-127 in their entirety and claims 30, 71 as they relates to an extra chromosome 21 Thus, claims 35-37, 39-42, 71, 76-78, 80-83, and 89 will not be searched as part of the mam invention because these do not include the first named species of chromosomal aberration or disease

The inventions listed as Groups 1-2 and the species listed as (i)-(xxix) and (xxx)-(lxi) do not relate to a single general inventive concept under PCT Rule 13 1 because, under PCT Rule 13 2, they lack the same or corresponding special technical features for the following reasons

With regard to the groups there is no special technical feature that joins the claimed inventions Turning to the first named invention in claim 1, for example, Lebo (US 5654148) teach a method of prenatal diagnosis comprising steps of providing a sample of amniotic fluid fetal DNA (Example I, Col 16, lines 10-46), analyzing the fetal DNA by hybridization to obtain fetal genetic information (Example VI, Col 18, lmes27-60), and based on the fetal genomic information obtained, providing a prenatal diagnosis (Example VI, Col 18, lines 61-67) Thus, since the first named invention is anticipated in the prior art, there is no special technical feature that joins the claimed inventions m view of the prior art Regarding the chromosomal aberration species, these species have in common only that they are aberrations wrthm the human genome It was known at the time the invention was made that aberrations in the human genome existed, as exemplified by Lebo who provides a method for detecting such aberrations Thus, the species listed regarding chromosomal aberrations are not joined by a special technical feature but instead each represent separate structural aberrations to be detected Likewise regarding the species of disease recited in the claimed invention, these are all diseases that do not share a common etiology or cause, other that that they are associated with genomic aberrations This is not a special technical feature that joins the species since diseases associated with chromosomal aberrations were known at the time the invention was made Therefore the lack of unity as set forth is proper

The first named which will be searched in accordance with the PCT rules is group 1, species group 1, regarding species (i) for the chromosomal aberration and species (xxx) for the disease or condition Thus, the claims searched with the main invention will be claims 1-29,-31,-32,-34,-38,-43-70,-72,-73,-75,-79,-84-88,-90-127-in-their-entirety-and-claims-30,-71-as-they-telates-te-an-extra-chromosome-^;

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Thus, claims 35-37, 39-42, 71, 76-78, 80-83, and 89 will not be searched as part of the main invention because these do not include the first named species of chromosomal aberration or disease.